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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,684	02/06/2007	Thomas Greiner-Stoffele	100728-56-WCG	4662

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EXAMINER	
BOESEN, CHRISTIAN C	
ART UNIT	PAPER NUMBER
4131	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,684	GREINER-STOFFELE ET AL.	
	Examiner	Art Unit	
	CHRISTIAN BOESEN	4131	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/20/2006 and 09/12/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Non-Final Office Action is responsive to the communication received 04/20/2006. Applicant's preliminary amendment filled 05/04/2007 is acknowledged and has been entered. Claims 1-15 are pending.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 04/20/2006 and 09/12/2007 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the Examiner. Please note the crossed out references are due to lack of English translations.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8, 10-11, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 recites the limitation "in step c)" in claim 7. There is insufficient antecedent basis for this limitation in the claim.

Claim 10 recites the limitation "the partial libraries in the compartments" in claim 7. There is insufficient antecedent basis for this limitation in the claim.

Claim 11 recites the limitation "the amplification of the partial libraries" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 15 recites the limitation "the test for a biocatalytic activity" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 and 7 and 9 and 12 and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by **Hubner** (Biochemistry, 1999, volume 38, page 1371).

Claims are drawn to a method for the identification of biomolecules in variant libraries.

Hubner discloses **claim 1(a)**, the production of variant library (page 1373 left column, center, "For library construction, we randomized the polypeptide segment between positions 42 and 46, which is mainly involved in guanine binding.")

Hubner discloses **claim 1(b)**, the division of the variant library by streaking the library out on agar plates with indicators (page 1372, right column, center, "Competent *E. coli* DH5αF'cells were prepared by the method of Inoue et al. (*31*), yielding a transformation efficiency of 5 x 10^7 colony forming units/μg of pB*R*322. Cells were transformed with 40 ng of the ligation mixture per 100 μL cell aliquot. Transformants were screened for RNA hydrolysis

activity on RNase indicator plates (*32*) containing Luria-Bertani medium supplemented with 100 mg of ampicillin, 75 mg of toluidine blue O, and 2 g of yeast RNA per liter.")

Hubner discloses **claim 1(c)**, the production of biomolecules in the transformed bacteria (page 1373, right column, center, "RNase variants were expressed and secreted by *E. coli* cells using the expression/secretion vector pA2T1, and active RNases could be detected on RNase indicator plates (*32*).")

Hubner discloses **claim 1(d)**, the selection of biomolecules on agar plates (page 1372, right column, center, "Colonies secreting active RNase variants could be identified by red haloes.")

Hubner discloses **claim 1(e) and (f)**, that the library can be divided and subjected to additional rounds of screening (page 1373, right column, center, "In several rounds of transformation and plating on RNase indicator plates, 180 active variants were detected from a total number of 1.6×10^6 independent transformants.")

Hubner discloses **claim 2**, selection for biocatalytic activity (page 1373, right column, center, "*Selection of Active Enzymes and Determination of Their Base Specificity.*")

Hubner discloses **claim 3**, amplification of the partial library, (page 1373, right column, center, "In several rounds of transformation and plating on RNase indicator plates, 180 active variants were detected from a total number of 1.6×10^6 independent transformants.")

Hubner discloses **claim 4**, dilution of the partial library (page 1373, right column, center, "In several rounds of transformation and plating on RNase indicator plates, 180 active variants were detected from a total number of 1.6×10^6 independent transformants.")

Hubner discloses **claim 5**, a variant library contains 10^3 to 10^{15} variants (page 1373, right column, center, "In several rounds of transformation and plating on RNase indicator plates, 180 active variants were detected from a total number of 1.6 x 10^6 independent transformants.")

Hubner discloses **claim 7**, the variant library is transferred into an organism before division (page 1373, right column, center, "RNase variants were expressed and secreted by *E. coli* cells using the expression/secretion vector pA2T1, and active RNases could be detected on RNase indicator plates (*32*).")

Hubner discloses **claim 9**, the organisms also conduct the production of the biomolecules (page 1373, right column, center, "RNase variants were expressed and secreted by *E. coli* cells using the expression/secretion vector pA2T1, and active RNases could be detected on RNase indicator plates (*32*).")

Hubner discloses **claim 12**, a variant library consists of DNA-plasmids, which contain the gene sequence coding for the biomolecule (page 1373, right column, center, "RNase variants were expressed and secreted by *E. coli* cells using the expression/secretion vector pA2T1, and active RNases could be detected on RNase indicator plates (*32*).")

Hubner discloses **claim 14**, the biomolecules are enzymes or ribozymes or other biomolecules, which exhibit a biocatalytic activity (page 1373, right column, bottom, "The hydrolysis profiles analyzed indicated that the RNase T1 variant RNase T1-8/3 (K41S/N43W/N44H/Y45A/E46D) was cleaving substrates with guanine and adenine in the 5' position, whereas all other variants still exhibited exclusively guanine specificity.")

Thus, by this disclosure Hubner anticipates the present claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6, 8, 11, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hubner (Biochemistry, 1999, volume 38, page 1371) as applied to claims 1 and 7 in combination with **Selifonov** (WO 01/12791 A1).

Claims are drawn to a method for the identification of biomolecules in variant libraries.

While Hubner teaches a method for the identification of biomolecules in variant libraries, as discussed above, Hubner does not teach that the variant library is divided up in 10^1 to 10^4 compartments, or that the culture of the organism after division is amplified to a number of organisms of 10^8 to 10^9 per compartment, or the partial libraries in the compartments are re-

isolated from the organisms, or the amplification of the partial libraries and the production of the biomolecules is conducted by cell-free systems, or the variant library consists of linear nucleic acid molecules, which contain the gene sequence coding for the biomolecule.

Stelifonov teaches **claim 6**, the variant library is divided up in 10^1 to 10^4 compartments (page 95, line 34, "To increase the chances of identifying a pool of sufficient size, a prescreen that increases the number of mutants processed by 10-fold can be used. The goal of the primary screen will be to quickly identify mutants having equal or better product titers than the parent strain(s) and to move only these mutants forward to liquid cell culture for subsequent analysis.")

Stelifonov teaches **claim 8**, that the culture of the organism after division is amplified to a number of organisms of 10^8 to 10^9 per compartment (page 40, line 3, " The starting DNA segments are recombined by any of the sequence recombination formats provided herein to generate a diverse library of recombinant DNA segments. Such a library can vary widely in size from having fewer than 10 to more than 10^5, 10^9, 10^{12} or more members.")

Stelifonov teaches **claim 11**, the amplification of the partial libraries is conducted by cell-free systems (page 22, line 20, " Alternatively, initial diversity can be induced, e.g., the variant forms can be generated by error-prone transcription, such as an error-prone PCR or use of a polymerase which lacks proof-reading activity (see, Liao (1990) Gene 88: 107-111), of the first variant form, or, by replication of the first form in a mutator strain (mutator host cells are discussed in further detail below, and are generally well known)." and page 5 line 24, "If

sequence recombination is performed *in vitro*, the recombinant library is preferably introduced into the desired cell type before screening/selection.")

Stelifonov teaches **claim 13**, the variant library consists of linear nucleic acid molecules (the products of PCR), which contain the gene sequence coding for the biomolecule (page 22, line 20, " Alternatively, initial diversity can be induced, e.g., the variant forms can be generated by error-prone transcription, such as an error-prone PCR or use of a polymerase which lacks proof-reading activity (see, Liao (1990) Gene 88: 107-111), of the first variant form, or, by replication of the first form in a mutator strain (mutator host cells are discussed in further detail below, and are generally well known).")

The present claims would have been obvious because the **substitution** of one known element 10-fold, taught by Stelifonov for another (quantity not specified), taught by Hubner would have yielded predictable results to one of ordinary skill in the art at the time of the invention (i.e. a 10-fold division of the variant library). See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

The present claims would have been obvious because the **substitution** of one known element 10 to more than 10^5, 10^9, 10^{12} or more members, taught by Stelifonov for another 1.6 x 10^6, taught by Hubner would have yielded predictable results to one of ordinary skill in the art at the time of the invention (i.e. a library of organisms of 10^8 to 10^9). See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

The present claims would have been obvious because the **substitution** of one known element *in vitro*, taught by Stelifonov for another *in vivo*, taught by Hubner would have yielded

predictable results to one of ordinary skill in the art at the time of the invention (i.e. *in vitro* amplification of libraries). See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

The present claims would have been obvious because the **substitution** of one known element linear nucleic acid, taught by Stelifonov for another vector nucleic acid, taught by Hubner would have yielded predictable results to one of ordinary skill in the art at the time of the invention (i.e. linear nucleic acid libraries). See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Thus, the present invention would have been *prima facie* obvious at the time the invention was made.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hubner (Biochemistry, 1999, volume 38, page 1371) as applied to claims 1 and 7 in combination with **Napolitano** (The Journal of Neuroscience, 1987, volume 7, page 2590).

Claims are drawn to a method for the identification of biomolecules in variant libraries.

While Hubner teaches a method for the *in vivo* expression of biomolecules, as discussed above, Hubner does not teach the *in vitro* expression of biomolecules.

Napolitano teaches **claim 10**, the *in vitro* protein expression of biomolecules starting with a cDNA clone (page 2595, left column, bottom, "NF-M mRNA was transcribed *in vitro* using the pNF-M2D insert subcloned into the pGEM system.")

The present claims would have been obvious because the **substitution** of one known element *in vitro* protein expression, taught by Napolitano for another *in vivo* protein expression, taught by Hubner would have yielded predictable results to one of ordinary skill in the art at the time of the invention (i.e. *in vitro* expression of biomolecules). See *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

All the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Thus, the present invention would have been *prima facie* obvious at the time the invention was made.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hubner (Biochemistry, 1999, volume 38, page 1371) as applied to claim 1 in combination with **Korn** (Methods in Enzymology, 2001, volume 341, page 142).

Claims are drawn to a method for the identification of biomolecules in variant libraries.

While Hubner teaches a method for the identification of biomolecules in variant libraries, as discussed above, Hubner does not teach that the test for a biocatalytic activity is conducted with fluorescence correlation spectroscopy.

Korn teaches **claim 15**, that the test for a biocatalytic activity is conducted with fluorescence correlation spectroscopy (page 142, top, "To investigate ribonuclease (RNase)-mediated cleavage of its presumed natural substrates - long RNA molecules - a variety of different assays have been developed" and page 142, bottom, "Furthermore, we present two assays to study the degradation of larger RNA substrate molecules using either methylene blue or fluorescence correlation spectroscopy (FCS).")

It would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to use Korn's ribonuclease assay in Hubner's method for the identification of biomolecules in variant libraries **to arrive at applicant's invention with the above cited references before them.**

One would have been motivated to use Korn's ribonuclease assay because Korn teaches "Binding, accumulation, and cleavage processes can be easily followed by FCS bases on the relation of the molecular weight and diffusion times of the molecules." (page 148, middle).

One would have had a reasonable expectation of success to assay ribonuclease activity because this assay is well established in the art as evidenced by Korn (page 151, top, "Table I, Diffusion times of rhodamine B-labeled deoxyribonucleotide (dOligo) and hetereoduplexes")

Thus, the present invention would have been *prima facie* obvious at the time the invention was made.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTIAN BOESEN whose telephone number is 571-270-1321. The examiner can normally be reached on Monday-Friday 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CHRISTIAN BOESEN/

Examiner, Art Unit 4131

/James O.Wilson/

Supervisory Patent Examiner, AU 1624